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Relation of Pulse Pressure to Blood Pressure Response to Exercise in Patients with Hypertrophic Cardiomyopathy

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Abstract

Almost one-third of patients with hypertrophic cardiomyopathy (HC) have an abnormal blood pressure response (ABPR) to exercise and this is associated with a greater risk of sudden cardiac death (SCD). In this study, we examined the association between steady (mean arterial pressure) and pulsatile (pulse pressure) blood pressure components as they relate to ABPR in patients with HC ($n = 70$). All patients completed a standard Bruce protocol during symptom limited stress testing with concurrent hemodynamic measurements. PP was significantly higher in HC patients with ABPR ($n = 19$) compared to HC patients with a normal BP response to exercise ($p < 0.05$). According to binary logistic regression, resting PP was a significant predictor of ABPR in patients with HC ($p < 0.05$). MAP was not significantly different between groups, nor was it a predictor of ABPR in HC. Those within the highest tertile of resting PP were 4.8 times more likely to have an ABPR compared to those within the lowest PP tertile (95% CI = 1.24 – 18.2, $p < 0.05$). In conclusion, elevations in resting PP may identify HC individuals at higher risk for having an ABPR during exercise.

Approximately 30% of patients with hypertrophic cardiomyopathy (HC) have an abnormal blood pressure response (ABPR) to exercise categorized as a failure to increase (or a potential decrease) in systolic blood pressure with an increase in exercise intensity and this ABPR is associated with sudden cardiac death in HC^{1–4}. Blood pressure (BP) exhibits both pulsatile and steady components. The pulsatile component of BP, estimated by pulse pressure (PP), reflects the integration of left ventricular systolic function, large-artery stiffness, forward pulse wave genesis and pulse wave reflection. Arterial stiffness is an important determinant of net cardiovascular performance and cardiac energetics at rest and during exercise⁵. As such increased PP, a manifestation of altered ventricular-vascular coupling and increased pulsatile afterload, may be related to ABPR in HC, but this has yet to be examined. The purpose of this investigation was to test the hypothesis that resting pulse pressure would be associated with ABPR during exercise in patients with HC.

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Conflicts of interest: None

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Methods

Seventy patients with HC were recruited from the HC center at Tufts Medical Center. Diagnosis of HC was based on criteria put forth by the American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. All patients had LV hypertrophy (wall thickness ≥ 15 mm according to echocardiographic demonstration) associated with a non-dilated cavity in the absence of another cardiac or systemic disease that could produce this magnitude of hypertrophy. Exclusion criteria included severe valvular disease, recent myocardial infarction or unstable cardiac symptoms, peripheral vascular disease, heart failure, end stage disease with systolic dysfunction or left ventricular ejection fraction $<40\%$, severe arrhythmia, chronic obstructive pulmonary disease, recent exertional syncope, prior septal myectomy, alcohol septal ablation, or coexistent aortic stenosis. Coronary artery disease (CAD) was defined as the presence of ischemia or infarction on single-photon emission computed tomographic nuclear myocardial perfusion imaging or $> 50\%$ stenosis of an epicardial coronary artery by angiography. The presence or absence of hypertension (SBP/DBP $> 140/90$ mmHg or taking anti-hypertensive medication) and clinical symptoms were obtained in each patient from questionnaire/medical records. All subjects gave written informed consent and this study was approved by the institutional review board at Tufts Medical Center.

Patients underwent standard 2-dimensional transthoracic echocardiography for assessment of cardiac dimensions followed by a symptom-limited exercise test using a standard Bruce protocol with concurrent hemodynamic assessment. Blood pressure was measured with auscultation and sphygmomanometry. Resting measures were made with HC patients in the supine position following a brief quiet rest period. BP was measured thereafter at the end of exercise stage. ABPR was defined as a reduction in systolic blood pressure (SBP) during exercise relative to resting SBP or an inability to increase SBP > 20 mmHg during exercise. PP was calculated as systolic BP – diastolic BP. Patients were instructed to withhold all cardiovascular medications 24–72 hours before exercise testing.

Presence of LV outflow tract obstruction was assessed as previously described at rest, with Valsalva and during exercise⁶. LV outflow tract obstruction was defined as a peak instantaneous outflow gradient of ≥ 30 mmHg by continuous-wave Doppler echocardiography⁶. Systolic anterior motion (SAM) and mitral regurgitation were assessed semi-quantitatively (scale 0–4) as previously described⁶.

All data are reported as means $\pm$ SEM. A priori significance was set at $p < 0.05$. Normality of distribution was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Chi-square tests were used to compare categorical variables. Patients with and without ABPR were compared using analysis of variance (ANOVA) for normally distributed variables and Mann-Whitney U tests for variables that were not normally distributed. If demographic variables differed between groups, analysis of covariance (ANCOVA) was used to adjust for group differences. Patients were then separated into tertiles according to PP and binary logistic regression was used to examine predictors of ABPR (entered as a discrete variable).

Results

Baseline demographics are shown in Table 1. Nineteen patients had an ABPR ($\sim 27\%$). There were significant group differences in age ($p = 0.004$) and diuretic use ($p = 0.014$) between ABPR patients and patients with a normal BP response to exercise (Table 1). Resting PP was significantly higher in HC patients with ABPR compared to HC patients with a normal BP response to exercise ($p = 0.007$, table 1). Differences in PP remained after adjusting for age and diuretic use with ANCOVA (adjusted means: 63 mmHg vs. 52 mmHg,

$p = 0.028$). Differences in PP also remained after adjusting for medication use (adjusted for beta-blockers, calcium channel blockers, ACE inhibitors, Norpace and other anti-arrhythmic agents: 64 mmHg vs. 52 mmHg, $p = 0.008$). MAP was not significantly different between groups ($p = 0.738$, table 1).

Prevalence of ABPR was not different in HC patients with versus without LV outflow tract obstruction (30% vs 24%, $p = 0.601$). PP was not different in HC patients with versus without LV outflow tract obstruction (56 mmHg vs 54 mmHg, $p = 0.612$). There were no sex differences in prevalence of ABPR (men: 26% vs women: 30%, $p = 0.776$). There were no sex differences in PP (men: 56 ± 3 mmHg vs women: 51 ± 3 , $p = 0.264$).

When separating patients in tertiles according to PP, prevalence of ABPR was significantly higher in HC patients with the highest PP compared to the reference group and second tertile ($p = 0.008$). Fifty percent of patient within the highest tertile of PP (> 60 mmHg) had an ABPR, versus 13% and 17% in the second (range: 45–60 mmHg) and third (< 45 mmHg) tertiles, respectively. According to binary logistic regression, after adjusting for potential confounders (age, gender, LV wall thickness, LA size, anterior basal septal wall thickness, history of chest pain, history of syncope, family history of HC, LV outflow tract obstruction, CAD) resting PP was a significant predictor of ABPR in patients with HC ($p = 0.016$). HC patients with the highest resting PP were 4.8 times more likely to have an ABPR compared to those with the lowest PP ($\beta = 1.6$, Wald = 5.2, 95% CI = 1.24 – 18.2, $p = 0.023$). SBP, DBP and MAP were not significant predictors of ABPR.

Discussion

The novel findings of the present study are as follows: 1) HC patients with an ABPR to exercise have significantly higher resting PP compared to HC patients with a normal BP response to exercise; 2) resting PP is a significant predictor of ABPR during exercise in patients with HC. Our findings suggest that resting PP, but not traditionally assessed BP components of CV risk assessment (namely SBP and DBP) or the steady component of BP (mean arterial pressure), is a predictor of the hemodynamic response to exercise in patients with HC.

Exercise testing is an integral part of the algorithm in risk stratification and delivery of prophylactic therapy for HC⁷. ABPR to exercise is predictive of SCD in HC, and SCD is the most common cause of death in HC⁸. In the present study, HC patients with high resting PP were almost 5 times more likely to have an ABPR to exercise. In other populations, elevated PP is associated with LV hypertrophy⁹, impaired ventricular relaxation¹⁰, ischemia during exercise¹¹, heart failure¹², increased left atrial size¹³ and atrial fibrillation (AF)¹⁴, all clinically relevant facets of HC pathology. Therefore, HC patients with an elevated resting PP may be a particularly high risk cohort. Given the correlation between ABPR and risk of SCD in HC, elevated PP may help identify high risk patients within the HC cohort.

The underlying pathophysiology that causes ABPR in patients with HC appears to be multifaceted and proposed mechanisms include: LV systolic dysfunction¹⁵ with subsequent subendocardial myocardial ischemia^{16,17}, altered baroreflex-mediated modulation of autonomic outflow to the heart and vasculature (possibly related to aforementioned subendocardial myocardial ischemia)¹⁸ and subsequent altered vascular response to exercise (i.e. excessive fall in peripheral/systemic vascular resistance)¹⁹. It has also been suggested that lower exercise capacity and ABPR in HC may be related to diastolic dysfunction²⁰ and a blunted augmentation of stroke volume during exercise²¹. Although seemingly

paradoxical, these mechanisms may have a single underlying and unifying aetiology related to arterial stiffness.

Patients with HC have greater arterial stiffness compared to controls²² and arterial stiffness has been shown to be related to reduced exercise capacity in HC²³. Our findings expand upon previous work by noting that PP, a manifestation of stiffening of the conduit vessels coupled with augmented pressure from wave reflections, is associated with ABPR in HC. Left ventricular ejection of stroke volume into a stiff aorta coupled with early return of reflected pressure waves increases pulse pressure and cardiac energetic demand, reduces myocardial oxygen supply/consumption, reduces subendocardial perfusion²⁴, impairs cardiac systolic and diastolic function and blunts stroke volume genesis²⁵. Thus increased arterial stiffness and pulsatile afterload may offer insight into findings of LV systolic/diastolic dysfunction, reduced stroke volume/cardiac output, reduced myocardial oxygen consumption and subsequent subendocardial ischemia contributing to ABPR in HC.

Finally, a strong relationship exists between arterial stiffness and integrated neural control of BP within the baroreflex arc. Stiffening of the vessels housing barosensory regions may depress mechanotransduction, resulting in a reduction of baroreceptor afferent firing per given unit of arterial pressure change, less inhibition of sympathetic outflow (altering peripheral vascular tone), and lessened amplification of cardiac vagal tone (altering LV contractility)²⁶. Indeed HC patients with hemodynamic instability during lower-body negative pressure, a HC cohort with higher prevalence of ABPR, have lower resting baroreflex sensitivity and exaggerated changes in baroreflex sensitivity during lower-body negative pressure¹⁹. Thus increased arterial stiffness in HC may also alter baroreflex modulation of cardiac and vascular autonomic control contributing to ABPR.

Similar to previous observations, prevalence of ABPR was not influenced by LV outflow tract obstruction^{1,2}. Previous studies have noted that LV outflow tract obstruction does not affect peripheral vascular endothelial function or vascular stiffness in HC^{22,27}. As such, LV outflow tract obstruction did not influence PP in the present study. We noted no sex difference in ABPR in HC and this too is consistent with previous reports¹. The lack of effect of sex on ABPR may be related to the observation that men and women within the age range studied tend to have similar brachial PP²⁸. Thus, LVOT obstruction and sex do not modulate PP in HC and as such, may not be significant determinants of ABPR during exercise in HC.

Few therapeutic options are available to attenuate the hypotensive BP response to exercise in patients with HC. Thamen *et al.* previously reported that neither propranolol nor clonidine significantly modulated the hypotensive BP response to exercise in HC¹⁹. However the selective serotonin reuptake inhibitor paroxetine was able to normalize the BP response to exercise¹⁹. Although the mechanism for this interaction remains unknown, paroxetine may have a favorable effect on vascular function^{29,30}. This raises the intriguing possibility that therapies that improve vascular function in HC may favorably affect the BP response to exercise.

Limitations to this study include lack of information on clinical endpoints and examination of a single surrogate marker (i.e. ABPR). Whether HC patients with elevated PP are truly a high risk cohort remains to be elucidated empirically. We used PP as an indirect measure of arterial stiffness. Additional research is needed to corroborate present findings using more valid bioassays of arterial stiffness such as pulse wave velocity.

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Table 1

Hypertrophic cardiomyopathy patient characteristics according to blood pressure response.

<i>Variable</i>	All	Abnormal Blood Pressure Response	Normal Blood Pressure Response
Age (years)	45±2	54±5	41±2*
Female	23 (33%)	7 (37%)	16 (31%)
Maximum LV thickness (mm)	19.6±0.6	20.0±1.1	19.5±0.6
Left ventricular end diastolic diameter (mm)	43.2±0.8	41.3±1.3	43.9±1.0
Left ventricular end systolic diameter (mm)	25.0±0.7	25.2±1.4	25.0±0.9
Left atrial size (mm)	39.8±0.9	40.5±1.5	39.6±1.0
Systolic anterior motion (scale 0–4)	1	1	1
Mitral regurgitation (scale 0–4)	1	1	1
Left ventricular outflow tract obstruction	33 (47%)	10 (52%)	23 (45%)
New York Heart Association Class			
I	41 (59%)	10 (52%)	31 (61%)
II	16 (23%)	3 (16%)	13 (25%)
III	13 (19%)	6 (32%)	7 (14%)
Medications			
β-blocker	41 (59%)	14 (74%)	27 (53%)
Calcium channel blocker	26 (37%)	7 (37%)	19 (37%)
Diuretic	7 (10%)	5 (26%)	2 (4%)*
ACE inhibitor	12 (17%)	3 (16%)	9 (18%)
Anti-arrhythmic	7 (10%)	2 (11%)	5 (10%)
Family History HC	26 (37%)	9 (47%)	17 (33%)
History of chest pain	22 (31%)	6 (32%)	16 (31%)
History of syncope	12 (17%)	4 (21%)	8 (16%)
Coronary artery disease	17 (24%)	6 (32%)	11 (22%)
Resting heart rate (bpm)	74±2	72±4	75±2
Resting systolic blood pressure (mmHg)	126±2	131±5	125±2
Resting diastolic blood pressure (mmHg)	70±2	67±2	71±2
Resting mean arterial pressure (mmHg)	88±2	89.0±3	88±2
Resting pulse pressure (mmHg)	55±2	64±5	52±2*

Values are mean ± standard error of the mean, unless otherwise indicated;

* significant group difference (p<0.05).